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Rituximab Maintenance Therapy to Treat Rheumatoid Arthritis

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Background

Rituximab (Rituxan) is a B lymphocyte-depleting drug that binds specifically to the transmembrane antigen CD20. In combination with methotrexate, it is indicated "to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies."[1] The recommended dosage of rituximab is 1,000 mg administered by intravenous infusion. A second dose of 1,000 mg is administered two weeks following the first dose. Retreatment 24 weeks after the first course of treatment is indicated in cases of residual disease.[1]

In 2007, CADTH's Common Drug Review considered rituximab for moderately to severely active rheumatoid arthritis. CADTH's expert committee recommended that "rituximab, when used in combination with methotrexate, be listed for the treatment of adult patients with severely active rheumatoid arthritis who have failed to respond to an adequate trial of an anti-TNF agent."[2] The drug expert committee noted that the evidence for the effectiveness and safety of repeated doses of rituximab was insufficient. Retreatment was recommended to be considered only in patients who achieved a response followed by a loss of effect, and after an interval of no less than six months since the previous dose.[2] Hence, the recommendation restricted the patient population to those with severe disease, and repeated treatment was only recommended to patients with an initial response to rituximab who subsequently experienced a relapse or a flare of their symptoms.

Policy Issue

Government-sponsored drug plans' reimbursement criteria for rituximab are generally in line with the recommendations of CADTH's expert drug committee. Clinicians would like to prescribe rituximab for maintenance therapy, as regularly scheduled treatment or at extended non-regular intervals, to prevent relapses or flares in patients who have had an initial response to rituximab. However, rituximab is not indicated for regular administration in the absence of disease activity or to prevent flares. There is need to review the evidence on the effectiveness and safety of rituximab administered as maintenance treatment.

The policy question is: *Should the reimbursement criteria be changed to permit the administration of rituximab at fixed intervals in patients with rheumatoid arthritis?*

Findings

A Rapid Response was commissioned to review the evidence on the efficacy and safety of rituximab administered as maintenance therapy in patients with moderately to severely active rheumatoid arthritis. The research question of the Rapid Response was: *What is the clinical effectiveness of rituximab maintenance therapy to treat patients with rheumatoid arthritis?* The literature was searched for English-language documents published between January 1, 1997 and May 30, 2018. Table 1 provides the selection criteria used to identify the relevant literature of population, intervention, comparators, outcomes, and study designs for the Rapid Response.

Table 1: Selection Criteria Used in the Rapid Response

Population	Patients (adults and children) with moderate to severe rheumatoid arthritis who have taken at least one dose of rituximab and have had a response to the treatment
Intervention	Rituximab at any dose given at regular intervals as maintenance therapy
Comparators	• Rituximab given at a disease flare or increased disease activity • Another drug as maintenance therapy • No comparator
Outcomes	*Effectiveness*: Disease activity, remission, joint count, function, patient-reported outcomes such as pain, fatigue, HRQoL *Safety*: Infections, other adverse events
Study Designs	• Health technology assessments, systematic reviews, meta-analyses • Randomized controlled trials • Non-randomized studies

HRQoL = health-related quality of life.

Table 2 provides the findings of the five studies meeting the inclusion criteria: two non-randomized comparative studies and three single-arm studies. For detailed information on the methods and findings, please refer to the Rapid Response report published on the CADTH website: https://cadth.ca/sites/default/files/pdf/htis/2018/RC0997%20Rituximab%20for%20Maintenance%20Therapy%20Final.pdf

Table 2: Results of the Studies Included in the Rapid Response

Study, Population, and Interventions	Results[a]	Of Note
Comparative Studies		
Chatzidionysiou, 2017 [3] Prospective cohort N = 800 **Population:** Treatment-experienced adult patients (inadequate response to non-biologic and/ or biologic DMARD) with high disease activity at start of treatment **Intervention:** RTX first cycle: two infusions of 1,000 mg, administered with a two-week interval RTX retreatment (two courses): fixed interval **Comparator:** RTX retreatment (two courses): on-flare Up to a total of three cycles	**DAS 28 (adjusted)[b]** There was a statistically significant difference between the on-flare and fixed-interval treatment groups, favouring the fixed-interval treatment group. Neither treatment groups achieved low disease activity (DAS 28 < 3.2). *1st retreatment —mean (95% CI):* • *Fixed interval: 3.8 (3.6 to 4.1)* • *On-flare: 4.6 (4.5 to 4.7)* *P* < 0.0001 *2nd retreatment — mean (95% CI):* • *Fixed interval: 3.7 (3.3 to 4.0)* • *On-flare: 4.6 (4.4 to 4.8)* *P* < 0.0001	Baseline DAS 28 score was statistically significantly worse for the on-flare treatment group for both retreatment periods. Baseline HAQ score was statistically significantly worse for the on-flare treatment group for the first, but not the second, retreatment period. Treatment was limited to three cycles (two retreatments). For the first retreatment, the median months from rituximab start was 7.5 months and 6.5 months for the on-flare and the fixed-interval groups, respectively. For the second retreatment, the median months from rituximab start was 18.5 months and 13 months for the on-flare and the fixed-interval groups, respectively. The retreatment doses were not stated.
Quartuccio, 2015 [4] Retrospective cohort N = 102 **Population:** Treatment-experienced adult patients (inadequate response to non-biologic and/ or biologic DMARD) with moderate to severe RA **Intervention:** RTX First cycle: dose of 1,000 mg, two weeks apart **RTX retreatment:** Fixed: dose of 1,000 mg, two weeks apart, at month 6 and subsequent courses	**DAS 28** There was no between-group difference in disease activity at 6 months, 12 months, or 24 months. Neither treatment group achieved low disease activity at any of the time points. *Month 12: median (range)* • *Fixed: 4.0 (2.3 to 7.1)* • *As needed: 4.1 (1.7 to 7.7)* *P* = 0.86 *Month 24: median (range)* • *Fixed: 3.3 (2.3 to 7.0)* • *As needed: 3.4 (1.4 to 7.6)* *P = 0.91* **HAQ** There was a statistically significant difference between the treatment groups at 6 months and 12 months (but not 24 months) favouring the as-needed treatment group. The difference was clinically	The two groups were not comparable on important patient characteristics at baseline: The as-needed treatment group had higher disease activity and lower disability; a higher proportion of biologic-naive patients (~20%); and a higher proportion of patient with RF and/or anti-CCP (~20%). This group may not have been as far advanced in their disease (i.e., less disability, less exposure to previous biologics) but had more symptoms (i.e., more disease activity). The fixed-interval treatment group received a retreatment at month 6 and subsequent retreatments at month 12 or later if DAS 28 < 3.2. We don't know how many treatment cycles the as-needed treatment group received or the intervals between retreatments. Data were collected at baseline, months 6, 12, and 24.

Study, Population, and Interventions	Results[a]	Of Note
every 6 months if DAS 28 < 3.2 not achieved **Comparator:** RTX retreatment**:** As needed, dose of 1,000 mg, two weeks apart	important based on an MCID of 0.22.[5] *Month 12 — median (range)* • *Fixed: 1.8 (0 to 3.0)* • *As needed: 1.2 (0.1 to 3.0)* *P* = 0.0004 *Month 24 — median (range)* • *Fixed: 1.7 (0.1 to 2.3)* • *As needed: 1.2 (0.1 to 3.0)* *P* = 0.37 The fixed-interval treatment group went from severe/very severe disability at baseline, to moderate/severe disability at 6 month, 12 months, and 24 months. The within-group difference in HAQ score was greater for the fixed-interval group than the as-needed group (change from baseline in median HAQ score of 0.95 vs. 0.25, respectively).	
Single-arm Studies		
Boleto, 2018 [6] N = 134 **Population:** Adult patients on long-term RTX treatment for RA RTX first cycle: two infusions (either 2 doses of 500 mg or two doses of 1,000 mg, given two weeks apart) RTX retreatment: 500 mg or 1,000 mg routine single dose; time to retreatment was determined by physician based on clinical response	**Primary Outcome** The incidence of hypogammaglobulinemia (< 6 g/L) was 17.2%. • *< 6 g/L: 23/134 (17.2%); 2.7 events per 100 patient-years* • *< 4 g/L: no case* **Follow-up** Mean gamma globulin concentration decreased from 11.9 g/L (SD 3.8) at baseline to 9.0 g/L (SD 3.1) at the last rituximab infusion (difference of 2.8 g/L, *P* < 0.001). **Safety** Patients who developed hypogammaglobulinemia were more likely to develop a severe infection compared with patients who did not develop hypogammaglobulinemia [26% (6/23 patients) vs. 6% (7/111), *P* = 0.033] or cancer [17% (4/23) vs. 2% (2/111) *P* = 0.001].	The mean interval between rituximab infusions was 7.8 months (SD 4.9). Baseline gamma globulin concentration was lower in patients who developed hypogammaglobulinemia. Mean study follow-up was 79.5 months (SD 24.6)
Vassilopoulos, 2016 [7] N = 234 **Population:** Treatment- experienced adult patients (inadequate response or intolerance to one or more TNF inhibitors) with moderate to severe RA	Safety *Adverse events: 110/233 (47.2%); 48.36/100 patient-years (95% CI, 42.04 to 55.36)* *Serious adverse events: 25/233 (10.7%); 6.68/100 patient-years (95% CI, 4.47 to 9.59)* *Adverse events leading to withdrawal: 2.99/100 patient-years (95% CI, 1.59 to 5.12)* *Death: 3/233 (1.3%); 0.69/100 patient-years (95% CI, 0.14 to 2.02)*	Patients were included if they received retreatment every 6 to 12 months. Patients received up to 7 cycles of treatment. A total of 234 patients were initially enrolled in the study; by the 7th cycle of treatment, there were 8 patients left in the cohort. The study followed patients for a median of 27.7 months. The definition of hypogammaglobulinemia was not provided.

Study, Population, and Interventions	Results[a]	Of Note
RTX first cycle: 1,000 mg administered on the 1st and 14th day RTX retreatment: 1,000 mg administered on the 1st and 14th day and repeated every 6-12 months Up to a total of 7 cycles	The proportion of patients who experienced an adverse event, a serious adverse event, or an infection was higher in the first two cycles of rituximab treatment, and decreased over the next cycles. The incidence of hypogammaglobulinemia was 1.7%. Patients > 65 years old were statistically significantly more likely to experience an adverse event or a serious adverse event compared with patients < 65 years old. The rates of infection or serious infection were not statistically significantly different between the two age groups. *Incidence rate ratio for adverse events:* *1.53, 95% CI, 1.16 to 2.02, P = 0.002* *Incidence rate ratio for serious adverse events:* *2.88, 95% CI, 1.34 to 6.21, P = 0.005*	
Vancsa, 2013 [8] N = 77 **Population:** Adult patients with moderate to severe RA undergoing RTX treatment RTX first infusion: 1,000 mg, two weeks apart on days 1 and 15 RTX retreatment: 1,000 mg, two weeks apart on days 1 and 15, every six months regardless of clinical response At least five cycles in 24 months	**Primary Outcome** The proportion of patients achieving a good EULAR response increased with repeated rituximab treatment (52% of patients at 6 months, up to 84% of patients at 24 months; baseline values not reported). *EULAR (24 months):* • *Change DAS 28 >1.2 (good response): 83.8%* • *Change DAS 28 0.6 to 1.2 (moderate response): 12.9%* • *Change DAS 28 < 0.6 (no response): 3.3%* **Secondary Outcomes** The mean DAS 28 score decreased over the course of treatment, but at 24 months, the score was still not below 3.2 (low disease activity not achieved). *DAS 28:* • *Baseline: mean (SD) 5.36 (0.34)* • *24 months: mean (SD) 3.43 (0.31) P < 0.001* Withdrawal due to adverse events occurred in 10% (8/77) of patients.	Patients received 4 retreatment cycles every 6 months. Patients included initial non-responders.

[a] Results are presented by primary and secondary outcomes if specified in the publication.

[b] Adjusted for concomitant corticosteroids and conventional synthetic disease-modifying antirheumatic drugs.

Anti-CCP = anti-cyclic citrullinated peptide; CI = confidence interval; DAS 28 = disease activity score 28 joint count; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; MCID = minimal clinically important difference; RA = rheumatoid arthritis; RF = rheumatoid factor; RTX = rituximab; SD = standard deviation; TNF = tumour necrosis factor.

Conclusions and Implications for Decision-Making

Two non-randomized studies and three single-arm studies met the inclusion criteria. The populations studied included treatment-experienced adult patients with moderate to severe rheumatoid arthritis. No randomized controlled trials were retrieved; no studies included children.

The evidence of comparative effectiveness comes from two observational studies: a prospective cohort study and a retrospective cohort study. Both studies measured the effect of rituximab on disease activity. The prospective cohort study showed that there was a statistically significant difference between the on-flare and fixed-interval treatment groups, favouring the fixed-interval treatment group. However, neither treatment group achieved low disease activity. The retrospective cohort study showed no statistically significant difference in disease activity between the fixed-interval group and the as-needed group; neither treatment groups achieved low disease activity.

The retrospective cohort study measured the effect of rituximab on disability. There was a statistically significant difference between the fixed-interval treatment group and the as-needed treatment group at 6 months and 12 months (but not 24 months), favouring the as-needed treatment group. The difference was clinically significant based on a minimal clinically important difference of 0.22. It is important to note that the as-needed treatment group had lower disability at baseline compared with the fixed-interval treatment group.

Of the three single-arm trials, only one evaluated efficacy. It showed that the majority of patients achieved a good response to maintenance therapy according to the EULAR criteria, but the patients did not achieve low disease activity.

The safety of repeat rituximab administration was evaluated in the three single-arm trials. Adverse events and serious adverse events were more common in the first two cycles of rituximab treatment. One of the concerns with repeat administration of rituximab is the effect that it may have on immunoglobulin levels (IgM, IgG). One single-arm trial reported that the incidence of hypogammaglobulinemia was 1.7%. The study followed patients for approximately 28 months and did not define hypogammaglobulinemia. The incidence of hypogammaglobulinemia (defined as < 6 g/L) was 17.2% in another trial with a longer follow-up; patients who developed hypogammaglobulinemia were more likely to develop a severe infection or malignancy.

The overall quality of the evidence was low. Study limitations that need to be taken into consideration when interpreting the results include: the differences in baseline patient characteristics between treatment groups in the cohort studies, the lack of comparator groups in the single-arm studies, and the differences in the number of treatment cycles administered across studies.

Policy Implication

There is a paucity of high-quality evidence on rituximab administered as maintenance therapy. Its effectiveness for this use has not been firmly established and the optimal retreatment intervals are unclear. Hence, no conclusions can be made as to whether rituximab administered at fixed intervals to prevent flares achieves better patient outcomes compared with rituximab administered as needed to treat flares or active disease.

Possible policy options include:

1) No change to the existing reimbursement criteria. Rituximab would continue to be reimbursed as recommended, "when used in combination with methotrexate, be listed for the treatment of adult patients with severely active rheumatoid arthritis who have failed to respond to an adequate trial of an anti-TNF agent. Rituximab should not be used concomitantly with anti-TNF agents."
2) Review requests on a case-by-case basis. Rituximab would be considered for maintenance treatment as a last resort in the most severe patients. Patients could receive rituximab to prevent flares at fixed intervals (e.g., every six months). Regular laboratory monitoring would be required for hypogammaglobulinemia.
3) Change the reimbursement criteria to allow patients to receive rituximab to prevent flares. Rituximab would be administered at fixed intervals (e.g., every six months). Regular laboratory monitoring would be required for hypogammaglobulinemia. Real-world evidence may be required to determine efficacy and to allow for reassessment.

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